

Injectable opioid treatment (IOT) expert group

Emerging consensus and advice to government

10 July 2009

INTRODUCTION

The vast majority of substitute opioid prescribing in England for the treatment of opiate (predominantly heroin) dependence is of oral medications: usually methadone or buprenorphine. Injectable substitute opioids are also available: principally diamorphine (pharmaceutical heroin) and an injectable form of methadone.

Injectable opioid treatment has been a long-standing, though relatively small-scale, form of treatment in England. This has usually taken the form of a relatively unsupervised treatment in which take-home supplies of an injectable medication are provided for the patient to inject away from the clinic or pharmacy.

There has been a growing body of research in the last decade which forms an emerging positive evidence base for the use of a fully supervised model of injectable opioid treatment (IOT) with some people who have severe and chronic opioid dependence, and have not responded to conventional oral substitute prescribing (usually with methadone or buprenorphine) or to abstinence-based treatments.

An expert group of clinicians, service users, commissioners, and academics (with input from policy officials) (see Appendix B) was convened in 2009 to:

- Review the provision of IOT, which has been a long-standing, though currently relatively small-scale, form of treatment in England
- Review evidence on IOT from the Randomised Injectable Opioid Treatment Trial (RIOTT), from other studies and experience in Europe and other countries, from a survey of clinicians in England and from the clinical experience of members of the group
- Discuss and aim to achieve consensus on the use of IOT for those with severe and chronic opioid dependence
- Consider a possible review of the NTA's 2003 expert guidance on IOT.

General principles that guided the deliberations of the 2009 IOT group

- Suitability and outcome: IOT must be shown to improve the outcomes of those patients for whom it is considered suitable – that is outcomes that cannot be achieved by conventional oral substitution treatment
- Clinical governance: Any model of IOT needs to be able to maintain clinical and community safety through clinical governance that protects individual patients and staff, and communities
- Cost effectiveness: IOT is a more expensive treatment than conventional oral opioid treatment and needs to be able to demonstrate that it provides benefits that merit this additional cost.

BACKGROUND TO CURRENT MODELS AND THEIR EVIDENCE BASE

Currently, in Britain there are two models of drug treatment that use injectable methadone and diamorphine: an existing and long-standing UK model and a new model currently being researched in some sites, based on developments in mainland Europe. These models and their evidence bases are briefly described below and summarised in Table 1.

A. Existing British model

In Britain, prescribing of injectable opioids (methadone or diamorphine) as substitutes for illicit heroin has been available for many years, but diamorphine prescribing has been restricted to licensed addiction specialists since the late 1960s. Current practice is that both medications are usually dispensed from pharmacies or clinics as take-home medication, with little supervision of use apart from perhaps a short period on initiation. Those on diamorphine usually continue in treatment in the long term and the number of prescriptions for diamorphine has remained low and reducing slightly over the last 15 years. Injectable methadone prescribing is more common but the number of prescriptions for injectable methadone has consistently and significantly reduced over the last 15 years, in the context of a substantial increase in oral methadone prescribing.

In 2003, the National Treatment Agency published guidance which aimed to improve the consistency of practice in this model, based on eight key principles, which were endorsed in the 2007 Clinical Guidelines.

Evidence: This model of delivery, with a pattern of prescribing take-home supplies of injectable medication, was subject to one randomised controlled trial (RCT) in the 1970s, published in 1980. There is clinical observational and anecdotal evidence of positive responses on this medication with long-term retention in treatment of some cases. However, this treatment is unique to Britain, and there is no new research trial of unsupervised injectable prescribing.

B. Fully supervised clinic model

In the 1990s, Switzerland adapted some of the clinical experience from the existing UK model and established, developed and evaluated on-site diamorphine consumption clinics. Similar clinics were later introduced and evaluated in other European countries and Canada, where there were developments of specific models of delivery of diamorphine and/or injectable methadone. This model is characterised by full supervision of all doses in specialist clinics, often with people attending two or three times per day. Take home doses, if prescribed, are of oral medication only. Full supervision by its nature prevents diversion of these prescribed drugs into the community, allows use of high dose if required, enables management of adverse events, and encourages clients' engagement with and retention in drug treatment. It also includes all appropriate psychosocial interventions and management of physical health and mental health aspects. The essential requirements of this model were considered to be the full supervision of all doses, flexibility with use of take home oral doses to support wider life activities and the provision of competent well trained staff.

Evidence: This approach of full supervision of all injecting of prescribed opioid medications has been the subject of five published randomised trials in different countries over the last 15 years (see Appendix A for summary). The expert group also heard confidential presentations of findings from RIOTT, to be published later in 2009.

There is a high level of consistency in the manner in which the diamorphine prescribing treatment has been provided in the evaluated clinics. There is a consistent finding from these recent trials of benefit through reductions in illicit substance use and offending, and clinical improvement in health. This evidence shows that it is feasible to achieve improvement in a group of patients who have previously failed to benefit from more conventional oral substitution treatments.

Table 1: Summary of IOT models

A. Existing British model	B. Fully supervised clinic model
Take-home supplies of diamorphine and injectable methadone. Injected by the patient away from clinic and pharmacy using injecting equipment supplied.	All doses of injectable opiate injected by the patient within the clinic under supervision of staff. Take home supplies of oral methadone equivalent given on request.
Psychosocial treatment typically consists of key-working and case management but is variable in practice	Enhanced medical and psychosocial interventions usually part of the research clinic provision.
Evidence base: • one RCT involving fewer than 100 patients in 1970s • several observational and case control studies.	Evidence base: • 5 published RCTs across six countries since 1998, involving more than a thousand patients selected as failing on current orthodox treatments • RIOTT in England, reporting shortly.
Doses of injectable opiates tend to be more conservative, i.e. lower.	Higher doses of injectable opiate treatment are prescribed since the patient can be directly monitored to ensure compliance, individual safety and removal of possible diversion or abuse.
Eligible patients are those failing on optimal oral treatment but who are judged to be able to comply with and self-regulate take-home supplies of injectable opioid.	Eligible patients are those failing on optimal oral treatment but, additionally, this treatment can be considered for those more severely impaired and challenging who would not have been suitable for the existing British model of IOT.

CONSENSUS STATEMENTS

1. Optimised oral opioid treatment before injectable treatment

The expert group considered that a sustained attempt at optimised oral opioid substitution treatment is an essential precursor to the consideration of injectable opioid treatment for an individual patient. This provision of optimised treatment using oral methadone or buprenorphine is expected to be the more appropriate form of maintenance treatment for the majority of patients. The group acknowledged the positive evidence base for optimised oral treatment (OOT) though considered that more work needs to be done to clarify and communicate the components of OOT, and monitor its implementation.

The expert group recognised that this work was outside its remit but recommended a review and update of the advice on OOT in *Injectable heroin (and injectable methadone): Potential roles in drug treatment* (NTA, 2003) and *Drug misuse and dependence: UK guidelines on clinical management* (DH & devolved administrations, 2007), which consider the psychosocial elements of OOT, different substitute opioids and implementation.

2. The current evidence base

The expert group recognised the strong European research evidence for the effectiveness of full supervision models of injectable opioid treatment for a minority of injecting heroin misusers who fail optimised oral opioid treatment. Based upon hearing confidential preliminary results, the expert group expect the England Randomised Injectable Opioid Treatment Trial (RIOTT) to achieve results in keeping with the European and emerging Canadian evidence.

3. Target group

The expert group emphasised that IOT is a treatment only to be considered for the minority of patients who have not responded to a sustained period of optimised oral opioid treatment.

4. Outcomes

For most of the patients in this target group, the evidence clearly shows that fully supervised IOT results in improved retention in treatment, reductions in illicit drug use and offending, and clinical improvement in health.

5. Cost effectiveness

The expert group received peer-reviewed evidence on the cost effectiveness of injectable clinics from European studies (e.g. Dijkgraaf *et al*, 2005), which showed significant cost benefit from IOT compared to oral substitute treatment when IOT was given to “chronic, treatment resistant heroin addicts”. The most significant cost benefit was to communities in terms of reduced offending and therefore avoided criminal justice and victim costs. The expert group considered that this evidence would be transferable to the English supervised injectable opioid treatment clinics and await RIOTT data on operational costs and cost effectiveness in September 2009.

6. Commissioning

The expert group considered that there would be some challenges to localised commissioning of high cost, low volume IOT clinics, although it also recognised that it was usual for the NHS to commission more expensive treatment for those who do not benefit sufficiently on conventional regimens, when evidence exists that the more expensive treatment can produce benefit.

The group considered that the implementation of IOT would benefit from a centrally-driven and centrally-funded initiative and that this support would be necessary to ensure consistent implementation throughout England.

The group recognised that the commissioning of IOT should be part of local drug treatment systems and current processes of local needs assessment and treatment system planning. The development of new or adapted services to provide IOT would then need to be supported by clear business and clinical plans, these plans to include criteria for eligibility for IOT patients, and care pathways in and out of IOT treatment.

7. Models of delivery/supervision

The group recognised the importance of safety to the individual and community, and the need to prevent diversion. The expert group recognised that the significant evidence base for IOT on the whole was for clinical models that included total supervision of all injectables. The continued and total supervision of all injectable doses allowed the European clinics and RIOTT to treat patients with a high complexity of need on high doses while avoiding any risk of diversion by the patients receiving the treatment.

The group also recognised the observed clinical evidence of positive improvement in some who have been treated in the Britain over many years. The group considered that those already in this treatment should continue with this form of treatment if considered successful clinically, and if the treatment is provided in line with the guidelines in the 2003 expert guidance and, more recently, with the 2007 Clinical Guidelines.

The expert group considered that total supervision of injectables was the ideal for all those being initiated on to IOT. As a minimum, the supervision requirements should be consistent with the recommendations of the 2007 Clinical Guidelines for supervised consumption of oral opioid treatment. However, there was uncertainty as to the duration of injectable treatment, whether this should be a treatment to ensure stability or potentially long term, and the extent to which patients should be encouraged to change to non-injecting modalities as well as the issue of take home doses of injectables. It was considered that these issues could be further researched with further development of specific clinics.

8. The next phase of IOT

The expert group recommended a “phase two” of IOT involving an expansion in the number of clinics. These could usefully learn from the RIOTT clinics and explore different models of IOT clinics (e.g. in urban and semi-rural settings, with different numbers of patients, and linked to existing drug treatment services or other services, such as in-patient or poly-clinic settings) to maximise cost efficiencies.

These various demonstration clinics should involve careful evaluation of clinical outcome and cost effectiveness. The group considered that these clinics could usefully explore the duration of IOT and whether there were some patients for whom full supervision could be safely relaxed after the initial period of full supervision.

9. IOT guidance

The expert group considered that additional clinical guidance could give clinicians and commissioners further advice on best practice and required standards in the existing British model of IOT. This guidance could be developed following a review of the 2003 IOT guidance: *Injectable heroin (and injectable methadone): Potential roles in drug treatment* (NTA, 2003) and might supplement the 2003 guidance rather than seek to update it wholesale.

References

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- National Treatment Agency (2003). Injectable Heroin (and Injectable Methadone): Potential Roles in Drug Treatment. London: National Treatment Agency for Substance Misuse
- Lintzeris N (2009). Prescription of Heroin for the Management of Heroin Dependence: Current Status. *CNS Drugs* 2009; 23 (6): 463-476

Appendix A: A brief summary of the evidence from European trials

The expert group was able to review the national and international research literature into injectable opioid treatment. In the 1990s, the Swiss considered the clinical experience in the UK and undertook an observational study of almost 1000 patients. This established the model of on-site diamorphine consumption with intensive psychosocial support. This project included a randomised controlled trial, which was followed by others in Europe. There are now several randomised controlled trials, which were available for the expert group to consider. All of the studies have been in countries with well-established oral treatment (Table 2). Eligible patients are those who have not benefited from standard oral methadone treatment (and in the German trial a sub group who were highly resistant to engage in it). The trials have studied treatment delivered in purpose-designed and developed treatment provision, based on the Swiss model and allowing relatively high dose on-site consumption. Early in the development of this research, a Cochrane review (2005) considered the first three studies in Table 2. It was not possible at that stage to draw conclusions about the efficiency of injectable diamorphine, in large part reflecting the methodological heterogeneity of the studies.

Table 2: Randomised controlled trials of IOT

Study	Year	Sample size	Country
Hartnoll et al	1980	96	UK
Perneger et al	1998	24	Switzerland
Van den Brink et al ("CCBH-A")	2003	174	Netherlands
March et al	2006	62	Spain
Haasen et al	2007	1015	Germany
Schechter et al ("NAOMI")	2009	251	Canada
Strang et al	Awaited	127	UK

All the studies reported on retention in treatment, summarised in Table 3.

Table 3: Retention reported in randomised controlled trials of IOT

Study	Retention – oral methadone	Retention – injectable diamorphine	Difference in retention statistically significant?
Hartnoll et al	25%	75%	Yes
Perneger et al	92%	93%	No
Van den Brink et al	85%	72%	No
March et al	68%	74%	No
Haasen et al	56%	68%	Yes
Schechter et al	54.1%	87.8%	Yes

The Swiss study demonstrated a significant difference in self-reported illicit heroin use of 22% in the injectable diamorphine group and 67% in the oral methadone group. The Spanish study also reported on illicit heroin (8.3 out of 30 days use in the injectable diamorphine group and 16.9 out of 30 days' use in the oral methadone group), although this was not a significant difference. The German study used self-report data, urine drug results and hair analysis to measure continued illicit heroin use (and also required a less than 20% increase in stimulant use). It reported reduced illicit drug use in 69% of the injectable diamorphine group and in 55% of the oral methadone group, a significant result.

The outcome measure used in the CCBH-A (Netherlands) study was a composite assessment of treatment response, consisting of a 40% improvement in physical, mental or social status without a deterioration of 40% in any other domain or 20% increase in stimulant use. According to these criteria 57% of the injectable diamorphine group and 32% of the oral

methadone group were responders, again a statistically significant result. The NAOMI study measures response according to improvement of at least 20% in the illicit drug use or legal subscale of the European Addiction Severity Index, and found 67% responded in the injectable group and 47.7% in the oral methadone group, a significant response.

The studies demonstrate improvement in the diamorphine group in a number of outcomes including psychological wellbeing and crime. For every 100 patients receiving diamorphine treatment, between seven and 25 more patients will show these benefits compared with oral methadone treatment.

While the individual studies each report positive outcomes in favour of injectable diamorphine, it remains difficult to combine the data between studies. Further limitations come from difference in total equivalent opioid dose between the oral methadone and injectable diamorphine groups in the CCBH-A study. It remains possible that the improvement in the diamorphine group was a dose effect. In addition patients on diamorphine were treated in purpose designed units while the control group received treatment as usual. The German study also included a comparison of different psychosocial interventions. In this study a large number of those randomised to oral methadone dropped out following randomisation. Apart from the biological data collected in the German study, all illicit heroin outcome data is based on self report. The forthcoming UK study, RIOTT, addresses this important limitation since it measures illicit heroin in urinalysis as the primary outcome measure.

Cost effectiveness data has been reported for the CCBH studies (the injectable and inhaled study, combined). The analysis does not demonstrate immediate healthcare savings (QALY 0.788 for diamorphine groups and 0.73 for methadone group). However, there were clear savings to society resulting from reduced law enforcement costs and reduced damage to victims of crime (mean saving of €12,793 (€1083 to €25,229) per patient per year).

There have been many decades of clinical experience of treatment with injectable diamorphine and injectable methadone in the UK, although only one published randomised controlled trial. This study compared oral methadone with injectable diamorphine. Average illicit heroin use at follow up was 59% in the injectable diamorphine group and 64% in the oral methadone group, an average which disguises extremes within the methadone group between a group who stopped illicit use and a group who continued high levels of illicit use. This study is further limited in its contemporary relevance by the fact that the doses of diamorphine and methadone were low, no doses were supervised and the illicit heroin outcome measure was based on self-report. A number of other reports have been published from the UK, consisting of: a pilot study establishing the feasibility of comparing oral and injectable methadone, observational studies and a case control study. These studies do point to improvements in illicit drug use, psychological and physical well-being, though the research is not robust.

Appendix B: Expert group membership

- Dr Eilish Gilvarry (Chair) (addiction psychiatrist, Newcastle)
- Dr Alison Battersby (addiction psychiatrist, Plymouth)
- Dr Owen Bowden-Jones (addiction psychiatrist, Central and North West London)
- Jayne Bridge (nurse, Merseyside)
- Anne Charlesworth (commissioner, Rotherham)
- Tony Cooke (commissioner, Kirklees)
- Gaynor Driscoll (commissioner, Kensington and Chelsea)
- Anshu Hinton (pharmacist, Central and North West London)
- John Howard (service user representative, Reading)
- Dr Stefan Janikiewicz (GP, Wirral)
- Peter McDermott (service user representative and NTA board member)
- Dr Tracey Myton (addiction psychiatrist, Shropshire)
- Dr Louise Sell (addiction psychiatrist, Manchester)
- Dr William Shanahan (addiction psychiatrist, Central and North West London)
- Professor John Strang (addiction psychiatrist, National Addiction Centre)

Observers and secretariat:

- Annette Dale-Perera, National Treatment Agency for Substance Misuse
- Dr John Dunn, National Treatment Agency for Substance Misuse
- John McCracken, Department of Health
- Dr Mark Prunty, Department of Health
- David Oliver, Home Office
- Sandra Wallace, Scottish Government
- Dr Sarah Watkins, Welsh Assembly Government
- Steve Taylor, National Treatment Agency for Substance Misuse
- Alex Fleming, National Treatment Agency for Substance Misuse